Campaign manufacturing of highly active or sensitizing drugs: a comparison between the GMPs of various Regulatory Agencies

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Abstract

Background. Cross-contamination and mix-ups are among the problems which could have a negative impact on the quality of the finished product during the production of highly active or sensitizing drugs with campaign manufacturing. Standardised, validated procedures ensure quality standards are maintained during production. In spite of this, the operating conditions and applicability of methods adopted by the various regulatory agencies manifest significant differences which could consequently compromise the safety of the finished product. This work has analysed and compared the GMP of various Regulatory Agencies to examine issues connected to campaign manufacturing highly active or sensitizing drugs.

Methods. the GMP of the following Regulatory Agencies have been studied: EMA, CFDA, COFEPRIS, FDA, Health Canada, ANVISA, CDSCO, PIC/S and WHO. The study was carried out for the purpose of understanding which agencies consent to the use of campaign manufacturing for the following categories of medicinal products: hormones, immunosuppressants, cytotoxic agents, highly active pharmaceutical ingredients (APIs), biological preparations, steroids, sensitizing pharmaceutical materials, antibiotics, cephalosporins, penicillins, carbapenems and beta-lactam derivatives.

Results. The GMP of Health Canada, EMA, PIC/S and FDA show a number of similarities, starting with the fact that they allow campaign manufacturing for similar categories of pharmaceutical products after an appropriate risk evaluation has been performed. CFDA, WHO, ANVISA authorise campaign manufacturing in "exceptional circumstances", though they do not always define what they mean by this. COFEPRIS authorises campaign manufacturing for certain classes of drugs, while there is no mention of campaign manufacturing in the CDSCO regulations.

Conclusions. Quite a few significant differences have been found in the various regulations concerning the use of campaign manufacturing and the classes of drugs that can be produced with this method. In the light of this, it is obvious that efforts to harmonise legislation internationally have not yet been successful: currently, states can adopt different quality standards. The pharmaceutical industry could use this situation to its advantage by delocalising production on the basis of existing standards. The need to harmonise GMPs is a priority which must be achieved as soon as possible. *Clin Ter 2020; 171(1):e66-73. doi:10.7417/CT.2020.2191*

Key words: Good Manufacturing Practices, campaign manufacturing, highly active or sensitizing drugs, cross-contamination, mix-ups, Regulatory Agencies, Quality Risk Management

Introduction

The production of highly active or sensitizing drugs requires special rules, as accidental contamination with other materials could have serious consequences for the health of patients, who in some cases take them without a medical prescription or trusting what they read on social media (1-9), and because they could also represent an occupational hazard to personnel who come into direct contact with these substances during all phases of production (10-13). Among the greatest dangers related to the manufacture of any drug, and in particular during the production of those classed as highly active or sensitizing, are cross-contamination and mix-ups (14,15). These risks increase in campaign manufacturing, when different products are manufactured in the same plant at different times (16). Using this method means using the same equipment at different times, following rigorous cleaning procedures. At times it is in this production phase that non-professional, superficial, inadequate behavior (17-19), that can be attributed to work-related stress to bad lifestyle choices that can increase improper behaviour in healthcare workers (20-22), that serious contamination cases can occur.

These risks are higher in campaign manufacturing, where drugs are exposed to a high contamination risk. This production method can only be chosen when validated procedures, ensuring no residues remain after the different phases of production, are in place. On the other hand, manufacturing a product in dedicated structures creates a series of inconveniences at organisational and economical level, so their use must be limited to cases for which no alternative production methods are possible (eg: the use of dedicated equipment for some phases of the production cycle, cleaning validation between production phases, etc.), guaranteeing production is carried out according to acceptable quality standards.

Campaign manufacturing brings definite advantages to the pharmaceutical industry in more than one way, though it is necessary to proceed with care and adopt specific rules when this production process is chosen for manufacturing highly active or sensitizing drugs, given that their accidental introduction to other products could be highly dangerous for people's health (23,24). Despite this, as has already been stated, Good Manufacture Practices (GMPs) have not been

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harmonised globally, some States require specific conditions for the manufacture of certain substances while other States require different conditions.

The Pharmaceutical Quality System of a company must, in addition to guaranteeing the best operating conditions are in place before production commences, follow national legislation and in particular required operating conditions and safety requirements (25).

This work will examine the challenges that are associated with campaign manufacturing highly active or sensitizing drugs among different Regulatory Authorities, study and compare their GMPs and highlight differences and similarities with the aim of identifying those that are most up to date. Data could help to implement a universal protocol on the production campaign manufacture for these medicinal products.

Methods

In this study, the GMPs of the following Regulatory agencies have been analysed: Europe (EMA), China (CFDA), Mexico (COFEPRIS), United States (FDA), Canada (Health Canada) Brazil (ANVISA), India (CDSCO), PIC/S and WHO. Its aim is to determine which authorities allow campaign manufacturing and analyse differences between various agencies on the use of this method of production for the following categories of medicines: hormones, immunosuppressants, cytotoxic agents, highly active pharmaceutical ingredients (APIs), biological preparations, steroids, sensitizing pharmaceutical materials, antibiotics, cephalosporins, penicillin, carbapenems, beta-lactam derivatives.

Results

Requirements set by the Regulatory Agencies for the campaign production of highly active or sensitizing drugs.

China. The State Food and Drug Administration (CFDA) is the Chinese Regulatory Authority that is in charge of the safety management of food, cosmetics and pharmaceutical products. GMPs have been provided by the CFDA in the "Good Manufacturing Practice 2010" (26). Regulations suggest that campaign manufacturing is included among methods which can be used to prevent cross-contamination (Art. 192). Art. 46 states the need to use dedicated facilities (e.g. a dedicated air handling system) and equipment in the production of certain hormonal, cytotoxic and highly potent chemical products. However it is specified that "In exceptional cases, the principle of campaign working in the same facilities and equipment can be accepted provided that specific precautions are taken and the necessary validations are made". Regulations authorise campaign manufacturing, but only in exceptional cases for "certain" hormones, "certain" cytotoxins and "certain" highly active drugs.

The CFDA allows campaign manufacturing for everything except beta-lactams, biological preparations and contraceptive hormones, which require production in dedicated areas.

Brazil. The Agência Nacional de Vigilância Sanitária (ANVISA) provides the following guidelines: *"Technical*

Regulation of Good Manufacturing Practices of Drugs (2010), Resolution - RDC n. 17" (27). With regard to the use of campaign manufacturing, under art.125 this method can be used in exceptional cases only "Such as accidents (fire, flood, etc.) or emergency situations (war etc.)", taking all necessary precautions and executing the correct validation procedures (including cleaning validation).

Art. 256 specifies that campaign manufacturing is applicable, in exceptional cases, for the following categories of pharmaceuticals: penicillins, cephalosporins, carbapenems, certain beta-lactam derivatives, preparations with biological organisms, some antibiotics, certain hormones, cytotoxic substances and other highly active materials.

As campaign manufacturing can be used only for products listed under art.256 and then only in emergencies, it is effectively forbidden for the production of "certain" highly active pharmaceuticals and "certain" highly sensitizing drugs.

Canada. The regulatory agency that promotes GMPs in Canada is Health Canada (HC) via its publication: "Good manufacturing practices guide for drug products - GUI-0001, 2018" (28). Health Canada authorises the use of campaign manufacturing "On a product by product basis, proper justification is provided, validation is conducted, and rigorous validated controls and monitoring are in place that show that any risk of cross-contamination is minimized" (C.02.007). The only classes of drugs for which the Canadian agency requires dedicated production facilities are penicillins and cephalosporins. Regarding all other categories of highly active or sensitizing drugs, HC accepts the use of campaign manufacturing, as long as a case by case evaluation following Quality Risk Management procedures has been carried out.

USA. GMP regulations in the United States are enforced by the FDA through the Federal Register (mainly CFR Title 21, parts 210 and 211) and numerous industry guidelines. American GMP specifics are defined in the FDA regulations 21 CFR 210.1 where it is established that the rules cited contain the "Minimum current GMP" for production methods (29,30). Though CFR 21, under sections 211.42 and 211.46, mentions the need for the use of separate facilities for the manufacture of penicillins, in its "Guidance for Industry Non-Penicillin Beta-Lactam Risk Assessment a CGMP Framework" the FDA, referring to campaign manufacturing, states the following: "Manufacturing that is restricted to a specific class of beta-lactam compound (e.g., the cephalosporin family of products) generally would not mandate separate facilities and air handling systems, and could permit production campaigning and cleaning as sufficient control" (31). The FDA permits campaign manufacturing for drugs which are restricted to a specific class of beta-lactam. As for other categories of highly active drugs, both in the "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients" and the "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients _ Questions and Answers Guidance for Industry" the FDA re-iterates the fact that campaign manufacturing is acceptable when appropriate measures to limit risks are used; while isolated facilities should be used for the production of highly sensitizing materials (such as penicillin and cephalosporins) and their use should also be evaluated when

materials of an infectious nature or high pharmacological activity or toxicity (such as for example certain steroids or cytotoxins with anticancer properties) (32,33).

World Health Organisation (WHO). The World Health Organisation (WHO) is a specialised UN Agency that deals with international public health. Its requirements for the production of drugs containing highly active or sensitizing substances have been set out in the "WHO Technical Report Series, No. 957, Annex 2 (2010)", in the "WHO Technical Report Series, No. 957, 2010 Annex 3 (2010)" and in the "WHO Technical Report Series, No. 986, Annex 2 (2014)" and other specific guidelines (34-36). In "Annex 2" of the "Technical Report Series, No. 986, (2014)", the WHO expresses the need for dedicated self-contained areas for the production of highly sensitizing materials (eg: penicillins) or biological preparations (eg: living organisms) to reduce the risks of accidental cross-contamination; while for other products such as highly sensitizing materials, biological preparations such as living organisms, certain hormones, cytotoxic substances, and other highly active materials campaign production is allowed in "exceptional cases" (though these are not defined), in accordance with validated procedures (including cleaning procedures) (12.24).

Regarding biological products, in 2016 the WHO published specific guidelines which clarified statements it had made previously, stating that if the producer is able to permit effective cleaning and decontamination/sterilization the use of multi-product facilities is justified for this class of substances (9.1). In these cases, the WHO permits campaign manufacturing, a subject dealt with in great depth in these Guidelines, which underline issues of applicability and peculiarities. Currently the WHO forbids campaign production for highly sensitizing materials such as penicillins.

EMA. In Europe, the European Medicines Agency (EMA) harmonises GMP from the twenty eight members of the European Union in the Eudralex Volume 4 (23). Due to the number and complexity of its clauses, Eudralex Volume 4 should be considered a combination of the best and most current manufacturing procedures. As in HC guidelines, the EMA mentions the need to use QRM procedures to evaluate and control risks of cross-contamination in product manufacture (5.20). These evaluations should provide a base from which to establish the most appropriate technical and organisational measures, including the need to use dedicated self-contained areas or campaign production (5.21). Under point 5.9 we read that:"Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross contamination"; to this end, on November 20, 2014 the European Medicines Agency released specific guidelines establishing the appropriate toxicological assessment to identify cross-contamination risks in the manufacture of different products in the same facility (37). The only categories for which the EMA requires the use of dedicated structures are beta-lactams, as Eudralex Volume 4 states: "Scientific data from the toxicological evaluation does not support a controllable risk" (3.6) (23). Regarding other categories of highly active or sensitizing drugs, campaign production should be evaluated on a case-by-case basis, carrying out pharmacological and toxicological tests to establish risks.

Pharmaceutical Inspection Convention (PIC) and Pharmaceutical Inspection Co-operation Scheme (PIC/S)

PIC and PIC/S are international instruments used to improve cooperation in GMPs among regulatory authorities and the pharmaceutical industry. EMA and PIC/S work together to harmonise GMPs at an international level, share resources and avoid/prevent duplication of effort. The GMP PIC/S guide is equivalent to the EU's GMP Guidelines in terms of requirements. PIC/S authorises campaign manufacturing (after appropriate QRM processes have been undertaken) for all classes of highly active or sensitizing drugs with the exception of beta-lactam antibiotics, which require dedicated structures for their production (38). The "Guide to good manufacturing practice for medicinal products" (Part II) PIC/S lists other categories of highly active or sensitizing drugs for which production in dedicated facilities should be considered, such as "Certain steroids or cytotoxic anti-cancer agents"; as, however, this has not been made a requirement, campaign manufacturing for these categories is not forbidden (39).

India. The "*Central Drugs Standard Control Organization*" (CDSCO) is the Indian Regulatory Agency which, with the promulgation of *SCHEDULE M* "*Drug and Cosmetics Act*", contains GMPs for drugs and cosmetics (40). The NFB states the need for dedicated areas for the production of beta-lactams, highly active products, sexual hormones, certain antibiotics, cytotoxic and oncological products, but does not mention the use of campaign production for highly active of sensitizing drugs. In fact, campaign manufacturing is not regulated by Indian guidelines and is not applicable to the above-cited categories which require dedicated areas for their production.

Mexico. The Regulatory Authority that publishes Mexican GMPs is the "Comisión Federal Para la Protección contra Riesgos Sanitarios" (COFEPRIS) in the NOM-164-SSA1-2015 "Buenas prácticas de fabricación de fármacos" (41). Mexican GMPs allow the same equipment to be used in manufacturing as well as campaign manufacture of different categories of highly active or sensitizing drugs when appropriate measures to reduce the risk of crosscontamination have been established/adopted. COFEPRIS authorizes campaign production for immunosuppressants which do not exhibit high pharmacological activity or high toxicity. Campaign production is not consented for the following substances: penicillin, cephalosporins, cytotoxic agents, steroid hormones (androgens, estrogens, progesterone), biological preparations and microorganisms and for drugs with high pharmacological activity and high toxicity. Regulations state that dedicated, self-contained areas must be used for their production (42).

Discussion

Currently, various Regulatory Agencies (in particular, EMA, FDA and International Conference of Harmonization) and a number of scientific papers are focusing on "*Continuous manufacturing*", a method of production which brings significant economic benefits and also has a positive impact on the quality of the finished product (43-46). Using other/ different production methods is a choice pharmaceutical industries are free to make. Even though GMPs adopted by different States are substantially different, there are currently no studies which compare regulatory differences in campaign manufacturing for highly active and sensitizing drugs, and this is what we aim to correct with this paper.

The GMPs examined adopt different regulations for production campaigns. Some Regulatory Agencies consider it a valid method of production if validated cleaning procedures ensure the removal of contaminants (from previous production cycles or cleaning agents). Other Agencies do not however consider campaign manufacturing sufficient to guarantee a product that is up to standard.

Considerable similarities can be found in HC, EMA and PIC/S regulations, as all mention the necessity for QRM to ensure whether campaign manufacturing can be employed. The three Agencies authorise this method of production without limits "in exceptional cases", provided that, the following information is provided for each product: a valid justification for the choice and proof of convalidation processes, rigorous monitoring and minimal risk of cross-contamination through adequate cleaning processes (23,28,38). Though the FDA, just as the above-mentioned Agencies, requires a case-by-case evaluation, unlike the latter it authorises campaign manufacturing for the production of different drugs, as long as they are in the same class of beta-lactams (31).

Mexican GMPs mention the possibility of using campaign production for highly active or sensitizing materials, but on the other hand rule out its use for many classes of drugs, which need completely dedicated, self-contained areas for production (41). In its Good Manufacturing Practice 2010, the CFDA authorises campaign manufacturing but for "certain" hormones, "certain" cytotoxins and "certain" highly active drugs only in exceptional cases (regulations do not define which cases are exceptional) (26). Similarly, the WHO authorizes campaign manufacturing only in exceptional cases for specific classes of drugs, but regulations do not specify what circumstances come under the term "exceptional"; finally, regarding biological products, the WHO states very clearly the cases in which this production method is consented (16,36).

Using campaign manufacturing to produce highly active or sensitizing drugs is not mentioned in Indian GMP, while ANVISA authorizes it for high-risk pharmaceuticals in grave emergencies (war, fire, flooding) (26,40). It should be stressed that the Brazilian Agency is the only one to permit campaign manufacturing for different classes of beta-lactams, but only if it is needed.

In the light of the above, the following table showing differences and similarities among various Agencies can be seen below (Table 1).

The table shown above considers regulatory differences for campaign production among the Agencies though this study has shown differences also exist for specific classes of highly active or sensitizing drugs which can be produced following campaign manufacture regulations in different countries.

Each Agency lists specific categories, at times even different categories, for which production is necessary in dedicated facilities; in these cases, campaign manufacturing is effectively forbidden by the Agency, which recognises the difficulty of controlling production risks.

The following table (Table 2) synthesizes differences found among the various Agencies for all classes of drugs analysed in the study.

The comparison is made even more difficult by the use of terms such as "Certain", "Some", "Other" when defining segregation levels for different medicinal categories, and this is true in particular for many classes of highly active drugs. These terms are used without being properly defined and in these cases it is the pharmaceutical industry's job to perform a risk analysis in order to pinpoint the appropriate containment measure. The use of these adjectives without providing a clear explanation of their meaning obviously leaves a lot of room for individual interpretation, and this could potentially have a negative impact on both the safety and efficiency of the production processes. We have looked at this in another paper which we believe could add to this study in order to see which terms are used by which Agency, as well as the meaning given to each term (25).

Limitations of the study

This work has some limitations. One of these is represented by the fact of having analyzed the GMPs of some, but not of all, regulatory agencies of the world. However, the analyzed regulations are among the most representative at a global level. Certainly, there are other Authorities that with their respective GMPs could reflect an even more variegated and complex situation on an international level.

A further limitation, if it can be judged as such, is the need to extend the study to the actual application of the rules and regulations at the level of the individual State. This could be even more articulated in the case in which a Regulatory Body of a State presents an internal GMP regulation and simultaneously adheres to harmonizing Agencies like PIC/S.

Conclusions

This study has shown that, though the Agencies have made changes to their regulatory frameworks, there still exist significant differences concerning the applicability of campaign manufacturing to highly active or sensitizing drugs, as well as the classes of drugs for which each Agency allows this method of production. The literature contains no critical analysis of regulations and their directives for this type of production, which, while not being risk-free, could significantly reduce production costs.

Campaign production should be utilised only when adequate cleaning procedures and measures to reduce the risks of cross-contamination are adopted between production cycles, following a case-by-case evaluation and periodical check-ups. Therefore, regulations consenting its applicability in exceptional cases are obsolete, given that in this sort of situation the safety of a production cycle could be compromised by the emergency. Furthermore, some Agency regulations, including the WHO and CFDA, do not define what "exceptional circumstances" are, allowing plenty of

Conditions	Canada	China	Brazil	Mexico	India	USA	Europe	WHO	PIC/S
For the production of "certain" highly active medicines in exceptional circumstances, campaign manufacturing is acceptable in common areas as long as suitable precautions are taken and the necessary convalidation done.									
Campaign manufacturing is acceptable when, according to the type of product, a valid justification is provided, valid and rigorous controls and valid monitoring have been made and that it has been demonstrated that there will be a minimal risk of cross-contamination.									
The principles of campaign manufacturing, for the production of highly active or sensitizing ingredients, are acceptable only in exceptional circumstances such wars, fires etc.									
Campaign manufacturing is not mentioned as a limitation in the Handbook/Regulations.									
Cross -contamination must be avoided by using adequate technical/organisational measures: campaign manufacturing followed by adequate cleaning procedures ()									
Production that is limited to a specific class of beta-lactam compounds (for example products in the family of cephalosporins) generally does not require separate facilities or air handling systems, and campaign manufacturing could be allowed if suitable cleaning and control procedures are put in place.									

Table1. Summary of requirements in different guidelines for the production of drugs with campaign manufacturing.

room for interpretation. Even more worryingly, the Agencies which do not mention campaign manufacturing in their regulations and consequently do not regulate its applicability give producers free reign and risk compromising safety standards for operators and patients alike.

The study shows that to date, EMA, PIC/S, HC and FDA regulations leave room for a case-by-case risk evaluation following clear quality standards using QRM principles.

Producers operating in countries which enforce these regulations have to follow quality standards which currently ensure increased safety for operators and patients.

Differences were also noticed for those classes of medicines to which the principles of campaign manufacturing can be applied. The production of drugs belonging to different classes of beta-lactams is not authorised by any Agency, with the exception of ANVISA. It is currently difficult to

Composition	Brasil ANVISA	China CFDA	Mexico COFE- PRIS	USA FDA	European EMA	Canada HC	India CDSCO	wно	PIC/S
Hormones	X certain	X certain (contra- ceptives)	X (steroid hormo- nes)	X certain	X certain	X certain	X (sexual)	X certain	X certain
Immunosuppres- sants	x		X certain		X certain	X certain			X certain
Cytotoxins		X certain	x	X certain	X certain	X certain	x	X certain	X certain
Highly active pharmaceuticals	X certain	X certain	X certain	X certain	X certain	X certain	x	X certain	X certain
Biological prepa- rations		x	x	x	X certain	X certain	x	X certain	X certain
Steroids	x			X certain	X certain	X certain		X certain	X certain
Sensitizing products	X certain	X certain	X certain	X certain	X certain	X certain	x	x	X certain
Antibiotics	X certain				X certain	X certain	X certain	X certain	X certain
Cefalosporins		x	x	X (different classes)	x	x	x	X certain	x
Penicillins		x	x	X (different classes)	x	x	x	x	x
Carbapenems		x		X (different classes)	x	X certain	x		x
Beta- Lactam derivatives		x		X (different classes)	x	X certain	x		x

Table 2. Regulatory agencies and classes of drugs for which campaign manufacturing is not permitted.

show/prove that residues resulting from the production of this class of antibiotics are completely removed. The Brazilian Agency is the only one to authorise campaign manufacturing for different classes of beta-lactams, though in exceptional cases only; clearly, in emergencies the lack of appropriate facilities and machinery due to the fact that this type of production is not normally allowed ensures there is a high risk of cross-contamination. This particular regulation should be reviewed as soon as possible. Unlike ANVISA, the FDA authorises campaign manufacturing for beta-lactams within the same group and does not limit its use to exceptional cases, though valid cleaning procedures and controls must be employed.

Regarding all other groups of highly active or sensitizing drugs cited in this study, HC, EMA and PIC/S are the only agencies able to assign a specific operating procedure to each compound, authorising campaign production exclusively in the presence of the appropriate technical/organisational measures and validated cleaning procedures to guarantee this method is used safely.

In the light of differences found between the various regulations, when deciding which drugs considered "certain" should be produced in dedicated facilities and which should be produced in accordance with the principles of campaign manufacturing, the pharmaceutical industry should make use of QRM and adopt the latter method only when it is authorised by the agency and when procedures guaranteeing the risks of cross-contamination are in place.

Though agencies like PIC/S and the WHO were established for the purpose of harmonising existing regulations, when it comes to the production of highly active or sensitizing drugs with campaign manufacturing this objective has not yet been achieved, and there are still substantial differences among various regulations. Quality standards are therefore not globally consistent and could easily tempt a company to delocalise production, transferring certain facilities to countries which have looser GMP regulations, consequently reducing structural, design, equipment and management costs. This could translate into a finished product of lower quality and increase risks for the patient and industry workers. As a result, harmonizing GMPs as quickly as possible is necessary.

References

- Spacilova L, Klusonova H, Petrelli F, et al . Substance use and knowledge among Italian high school students. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2009; 153(2):163-8
- Grappasonni I, Scuri S, Tanzi E, et al. The economic crisis and lifestyle changes: a survey on frequency of use of medications and of preventive and specialistic medical care, in the Marche Region (Italy). Acta Biomed 2018 Mar 27; 89(1): 87-92. doi: 10.23750/abm.v89i1.7068
- Siracusa M, Grappasonni I, Petrelli F. The pharmaceutical care and the rejected constitutional reform: what might have been and what is. Acta Biomed 2017 Oct 23; 88(3): 352-359. doi: 10.23750/abm.v88i3.6376
- Signorelli C, Odone A, Gozzini A, et al. The missed Constitutional Reform and its possible impact on the sustainability of the Italian National Health Service. Acta Biomed 2017 Apr 28; 88(1): 91-94. doi: 10.23750/abm.v88i1.6408.
- Petrelli F, Contratti CM, Tanzi E, et al. Vaccine hesitancy, a public health problem. Ann Ig 2018 Mar-Apr; 30(2): 86-103. doi: 10.7416/ai.2018.2200
- Grappasonni I, Petrelli F, Klusoňová H, et al. Level of understanding of medical terms among italian students. Ceska Slov Farm. Winter 2016; 65(6): 216-220
- Scuri S, Petrelli F, Tanzi E, et al. European university students of pharmacy: survey on the use of pharmaceutical drugs. Acta Biomed 2019; 90 (1): 83-91. doi: 10.23750/abm. v90i1.7572
- Nguyen CTT, Scuri S, Nguyen BT, et al. Levels of understanding of the rules of correct medical usage among vietnamese pharmacy students: a cross-sectional study. J Prev Med Hyg 2018; 59 (4): E261-E266. doi: 10.15167/2421-4248/ jpmh2018.59.4.925.
- Scuri S, Petrelli F, Tesauro M, et al. Energy drink consumption: a survey in high school students and associated psychological effects. J Prev Med Hyg 2018; 59 (1): E75-E79. doi: 10.15167/2421-4248/jpmh2018.59.1.898
- Cioffi P, Marotta V, Fanizza C, et al. Effectiveness and response predictive factors of erlotinib in a non-small cell lung cancer unselected European population previously treated: a retrospective, observational, multicentric study. J Oncol Pharm Pract 2013 Sep; 19(3): 246-53. doi: 10.1177/1078155212465994. Epub 2012 Dec 7. PubMed PMID: 23223401
- Nguyen CTT, Petrelli F, Scuri S, et al. A systematic review of pharmacoeconomic evaluations of erlotinib in the first-line treatment of advanced non-small cell lung cancer. Eur J Health Econ 2019 Mar 6. doi: 10.1007/s10198-019-01040-7.
- 12. Cioffi P, Laudadio L, Nuzzo A, et al. Gemcitabine-induced posterior reversible encephalopathy syndrome: a case

report. J Oncol Pharm Pract 2012 Jun; 18(2): 299-302. doi: 10.1177/1078155211424628.

- Siracusa M, Scuri S, Grappasonni I, et al. Healthcare acquired infections: malpractice and litigation issues. Ann Ig. 2019 Sep-Oct;31(5):496-506. doi: 10.7416/ai.2019.2310.
- Sargent, Edward V, et al. The regulatory framework for preventing cross-contamination of pharmaceutical products: History and considerations for the future. Regulatory Toxicology and Pharmacology 2016; 79: S3-S10
- Minutillo A, Palmi I, Mastrobattista L. The health threat of drugs of abuse adulteration by new psychoactive substances. Clin Ter. 2019 Nov-Dec;170(6):e425-e426. doi: 10.7417/ CT.2019.2170
- WHO, "Good Manufacturing Practices for Biological Products". Technical Report Series, No. 996, Annex 3, 2016 (Replacement of Annex 1 of WHO Technical Report Series, No. 822)
- Siracusa M, Petrelli F. Trade of food supplement: food or drug supplement? Recenti Prog Med 2016 Sep; 107(9): 465-471. doi: 10.1701/2354.25224
- Grappasonni I, Marconi D, Mazzucchi F, et al. Survey on food hygiene knowledge on board ships. Int Marit Health 2013; 64(3):160-7
- Grappasonni I, Petrelli F, Scuri S, et al. Knowledge and Attitudes on Food Hygiene among Food Services Staff on Board Ships. Ann Ig 2018 Mar-Apr; 30(2): 162-172. doi: 10.7416/ai.2018.2207
- Petrelli F, Grappasonni I, Peroni A, et al. Survey about the potential effects of economic downturn on alcohol consumption, smoking and quality of life in a sample of Central Italy population. Acta Biomed 2018 Mar 27; 89(1): 93-98. doi: 10.23750/abm.v89i1.7059.
- Spáčilová L, Málková E, Hajská M, et al. Epidemiology of addictive substances: Comparison of Czech and Italian University students' experiencies. Chemicke Listy Vol 101, Issue 14, 2007, Pages s147-s150
- 22. Grappasonni I, Paci P, Mazzucchi F, et al. Awareness of health risks at the workplace and of risks of contracting communicable diseases including those related to food hygiene, among seafarers. Int Marit Health. 2012;63(1):24-31
- 23. EMA, "Eudralex Volume 4. Good manufacturing practice (GMP) Guidelines", 2015.
- Pirani F, Lo Faro AF, Tini A. Is the issue of Chemsex changing? Clin Ter. 2019 Sep-Oct;170(5):e337-e338. doi: 10.7417/CT.2019.2157
- Petrelli F, Caraffa A, Scuri S, et al. The requirements for manufacturing highly active or sensitising drugs comparing Good Manufacturing Practices. Acta Biomed. 2019 May 23;90(2):288-299. doi:10.23750/abm.v90i2.8340.
- CFDA. "People's Republic of China: Good Manufacturing Practice for Drugs" (2010 Revision) (MOH Decree No. 79).
- 27. ANVISA, "Technical Regulation of Good Manufacturing Practices of Drugs", Resolution – RDC n. 17, 2010.
- 28. Health Canada, "Good manufacturing practices guide for drug products GUI-0001", 2018.
- 29. US Food and Drug Administration. "CFR-code of federal regulations title 21." Current good manufacturing practice for finished pharmaceuticals Part 210 (e-CFR data is current as of June 23, 2019)
- US Food and Drug Administration. "CFR-code of federal regulations title 21." Current good manufacturing practice for finished pharmaceuticals Part 211 (e-CFR data is current as of June 23, 2019)

- US Food and Drug Administration. "Guidance for Industry - Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing CrossContamination" April 2013
- 32. FDA, "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients Guidance for Industry", 2016
- FDA, "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients _ Questions and Answers Guidance for Industry", 2018
- WHO, "WHO Good Manufacturing Practices for Active Pharmaceutical Ingredients". Technical Report Series, 2010 ;957, Annex 2
- WHO, "Good Manufacturing Practices for Pharmaceutical Products containing hazardous substances", Technical Report Series, No. 957 Annex 3, 2010
- WHO, "WHO Good Manufacturing Practices for Pharmaceutical Products: main principles", Technical Report Series, No. 986, Annex 2, 2014
- 37. EMA, "Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities", 2014
- PIC/S, "Guide to good manufacturing practice for medicinal products", PE 009-14 (Part I), 2018
- PIC/S, "Guide to good manufacturing practice for medicinal products", PE 009-14 (Part II), 2018

- CDSCO, Schedule M, "Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products", The Drugs And Cosmetics Act And Rules, India, 2005
- 41. COFEPRIS, Norma Oficial Mexicana NOM-164-SSA1-2015, "Buenas prácticas de fabricación de fármacos", 2015
- COFEPRIS, "Anexos a la Norma Oficial Mexicana NOM-SSA1-059-2015; Buenas prácticas de fabricación de medicamentos", 2014
- Allison G, Cain YT, Cooney C et al. Regulatory and quality considerations for continuous manufacturing May 20–21, 2014 Continuous Manufacturing Symposium. J. Pharm. Sci. 104(3), 803–812 (2015)
- FDA, "Quality considerations for continuous manufacturing guidance for industry. Guidance for Industry", Draft Guidance, 2019
- 45. Helal, Nada A. et al. "Integrated continuous manufacturing in pharmaceutical industry: current evolutionary steps toward revolutionary future." Pharmaceutical Patent Analyst 0, 2019
- Burcham CL. et al, "Continuous Manufacturing in Pharmaceutical Process Development and Manufacturing". Annu. Rev. Chem. Biomol. Eng. (2018) 9:253-281